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ABSTRACT

Objectives Little is routinely disclosed about the costs of the pivotal clinical trials that provide the key scientific evidence of the treatment benefits of new therapeutic agents. We expand our earlier research to examine why the estimated costs may vary 100-fold.

Design A cross-sectional study of the estimated costs of the pivotal clinical trials supporting the approval of 101 new therapeutic agents approved by the US Food and Drug Administration from 2015 to 2017.

Methods We licensed a software tool used by the pharmaceutical industry to estimate the likely costs of clinical trials to be conducted by contract research organizations. For each trial we collected 52 study characteristics. Linear regression was used to assess the most important factors affecting costs.

Primary and Secondary Outcome Measures The mean and 95% confidence interval of 225 pivotal clinical trials using varying assumptions. We also assessed median estimated costs per patient, per clinic visit, and per drug.

Results Measured as pivotal trials cost per approved drug, the 101 new molecular entities had an estimated median cost of $48 million (IQR $20 million - $102 million). The 225 individual clinical trials had a median estimate of $19 million (IQR $12 million - $33 million) per trial and $41 413 (IQR, $29 894-$75 047) per patient. The largest single factor driving cost was the number of patients required to establish the treatment effects and varied from 4 patients to 8442. Next was the number of trial clinic visits, which ranged from 2 to 166. Our statistical model showed trial costs rose exponentially with these two variables. ($R^2 = 0.696$, $F = 257.9$, $p < 0.01$).

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- To ensure our selection of new drugs was representative, our sample included all new therapeutic drugs approved over a recent three-year period.
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- The estimates assess a range of what a contract research organization might charge to conduct the study and do not include sponsor costs for study design, contract monitoring, or medication.
- These estimates do not reflect the total costs of developing a new drug, which include many other kinds of laboratory, animal, and human studies.

INTRODUCTION

The costs of conducting clinical drug trials are not among the extensive public disclosures now required by U.S. federal law,[1] the International Committee of Medical Journal Editors,[2] and other entities. When this project began in 2017, a literature search revealed a single published study assessing the costs of conducting individual clinical trials.[3] Nevertheless, this information is central to debates about whether requirements for testing a new drug to meet US Food and Drug Administration (FDA) or European Medicines Agency (EMA) are too burdensome, or the trials are so expensive that they justify high drug prices. To provide a factual foundation for this debate, we licensed a pharmaceutical industry cost estimating tool and began systematically collecting data about recent pivotal trials that supported FDA approval. Pivotal trials are those studies in humans that provide under US law "substantial evidence" of benefit to justify marketing approval.[4] They are the largest and most expensive studies in the cycle of drug development testing and are conducted to verify the existence of or measure the extent of benefits in the patient population expected to be treated. Pivotal trials also provide seminal information on safety, which is also assessed in Phase 1 studies of pharmacokinetic effects and in specialized safety studies where needed.

We previously published initial reports on a subset of these trials. [5,6]. For this study we expanded our trial data by 40% and for the first time analyzed cost per drug and focused on the reasons why costs of conducting clinical trials could vary by more than 100-fold.

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Study Data

We identified all new therapeutic agents from the 2015-2017 annual reports on Novel Drugs published by the FDA's Center for Drug Evaluation and Research.[7–9] We excluded agents for diagnostic, medical, and surgical procedures because these short-term exposures require notably different clinical testing. The pivotal trials that provided substantial evidence of benefit were those specifically cited in the standard FDA approval document, the Summary Review or Cross Disciplinary Review.

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We derived the estimates for each trial using the IQVIA CostPro Mid-Level Tool,[10] a clinical trial cost estimating program used by pharmaceutical manufacturers. Its estimates were derived from actual data from 2000 final awarded trial proposals and integrates cost information from 200,000 trial sites in 60 countries. For each trial CostPro produced a low, median, and high estimate based on industry benchmark data. The program also provided default values derived from industry benchmarks for occasional missing values, such as number of patients screened. The medical condition treated and related therapeutic areas were defined in the IQVIA CostPro Mid-Level Tool based on a subset of the International Classification of Diseases Version 9. Our preliminary investigation revealed that some trial costs are driven by trial conduct features that are not publicly available. This included the number of amendments to the trial protocol, the number of Institutional Review Boards, and how frequently sites were monitored. After consulting with experienced trialists, we computed two sets of estimates, one assuming more efficient trial conduct, and one less efficient. Our primary outcome variable was the mean (95% CI) of all six estimates, three from each efficiency assumption group. All costs were in current US dollars.

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We report the median and interquartile range (IQR) for most variables because they were not normally distributed. For assessing differences between categorical variables, we used a non-parametric test of significance, the Kruskal-Wallace rank sum tests. We used linear regression to model the relationship of trial cost with patients enrolled and patient visits but after log-transforming these variables to achieve a near-normal distribution. The R package for statistical computing, version 3.5.3, was used for all statistical analysis.

Review and Verification

Prior to collecting the data for this study, we conducted sensitivity analysis of the input variables for the CostPro Mid-Level Tool to assess each major variable and whether default values were calculated on the basis of the underlying source data from clinical site contracts. Some variables, such as the countries where trial sites were located and the specific disease condition being treated, proved to have a marked effect on estimated costs. Next, we tested the CostPro tool to compare our estimating methods with some of the available published estimates and determined that they were similar. Finally, we reviewed our preliminary methods and results with experienced clinical trialists with hands-on experience working with trial cost estimates.

Patient and public involvement

No patient involvement.

Results

Our data include 101 new drugs and 225 pivotal clinical trials that enrolled 156 140 patients who were studied for treatment effects in 2 241 401 clinic visits. Characteristics of the source trials data are shown in table 1.

Table 1 Patients, trials, and drug totals in pivotal trials

Totals by approval year				
	2015	2016	2017	Total
Drugs	40	19	42	101
Trials	86	52	87	225
Patients	69 050	28 111	58 979	156 140

Totals by trials per drug		
Trials per drug	Number of drugs	Total patients
1	45	49 022

2	29	32 157
3-11	27	74 961

Overall, the estimated cost of trials supporting the approval of 101 approved drugs was a median of $48 million (IQR $20 million - $102 million). The estimated costs per drug and by therapeutic area are shown in table 2. Each individual pivotal trial cost a median of $19 million (IQR $12 million - $33 million). The estimated cost per patient was $41 413 (IQR $29 894 - $75 047), and each patient visit to the study clinic cost an estimated median of $3685 (IQR $2640 - $5498).

Table 2 Per drug estimated trials costs by therapeutic area

Therapeutic area	Drugs	Median (IQR), US$ in millions
Blood	2	6 (4 - 8)
Cardiovascular	6	141 (74 - 183)
Central Nervous System	14	42 (16 - 85)
Dermatology	9	50 (31 - 77)
Endocrine/metabolism	12	72 (14 - 144)
Genitourinary	4	23 (12 - 37)
Gastrointestinal	7	31 (15 - 63)
Infectious	9	54 (26 - 102)
Musculoskeletal	2	68 (48 - 87)
Oncology	30	45 (29 - 72)
Ophthalmological	3	36 (34 - 44)
Respiratory	3	91 (73 - 110)
Overall	**101**	**48 (20 - 102)**

Costs per drug varied substantially by the number of pivotal clinical trials conducted to support marketing approval. Costs were generally lowest when the requirement for replication was waived and a single trial accepted. Overall, 45/101 (45%) of drugs were approved with a single trial with a median cost of $28 million (IQR $13 million – $62 million). As might be

expected, the replication requirement for 2 trials nearly doubled the estimated cost per drug of 29 other drugs to a median $45 million (IQR $28 million - $69 million). In addition, 27 drugs were approved with 3-11 clinical trials each at an estimated overall median cost of $91million (IQR $56 million - $128 million) per drug. The reason for three or more trials was because approval was sought for several closely related indications, often combination or adjuvant therapy.

From an individual clinical trial perspective, the largest single influence on estimated cost was the number of patients needed to establish the treatment effects. Although the trials enrolled a median of 495 patients there was wide variation, ranging from 4 patients to 8446 patients.The differences and variability within patient enrollment categories are shown in the boxplots in figure 1. It also shows that there were often outliers to the median estimates even after plotting the data on a log scale.

One factor requiring more patient enrollment was when already approved drugs were known to be effective for the indication sought. One measure of the availability of other effective drugs was the need for an active drug comparison group rather than an inactive placebo. The 62 trials with an active drug control group enrolled a median of 653 patients, compared to 547 patients for placebo control, and 145 patients in uncontrolled trials.

While the number of patients required was the most important cost driver, we also observed variation in the trial cost per patient. Treatments varied in intensity from eye drops and skin creams to infusions of multiple oncology drugs. Table 3 shows how cost per patent varied by therapeutic area.

Table 3. Per patient estimated pivotal trial costs by therapeutic area

Therapeutic area	Trials	Median (IQR), US$		
Blood	2	310 975	(200 213	- 421 738)
Cardiovascular	6	34 857	(22 922	- 50 540)
Central nervous system	33	39 467	(31 825	- 67 988)
Dermatology	21	24 861	(19 523	- 30 573)
Endocrine/metabolism	52	40 612	(34 874	- 63 420)
Genitourinary	7	39 640	(23 179	- 47 100)
Gastrointestinal	12	27 887	(25 633	- 55 687)
Infectious	31	37 175	(31 497	- 49 283)
Musculoskeletal	3	58 212	(34 811	- 63 447)
Oncology	39	100 271	(80 880	- 155 714)
Ophthalmological	9	23 893	(16 990	- 29 894)
Respiratory	10	53 590	(39 062	- 59 814)
Overall	225	41 413	(29 894	- 75 047)

The second-ranked influence on the estimated cost of the pivotal trials was the number of clinic visits required for screening, baseline randomization, treatment, and benefit assessment. The pivotal trials had a median 11 trial visits (IQR 8 - 17) and ranged from 2 to 166 visits. Each additional trial visit added a median of $2 million (IQR $1 million - $3 million) to the overall estimated trial cost. More trials visits could reflect greater intensity of treatment as well as longer duration of treatment or observation.

The results of linear regression predicting estimated trial costs based on the number of enrolled patients and the number of trial visits are shown in figure 2. This combination of just these two variables into individual patient clinic visits explained 69% of the variation (R^2) in estimated costs of pivotal trials. Both dependent and independent variables were log transformed to normalize the distribution. Analysis of variance showed the number of patients explained more than three times as much variation as the number of visits. Additional regression details are shown in figure 2.

Discussion

Our study shows that the cost burden of conducting pivotal trials is driven by two central questions: 1) How many patients are needed to show a drug benefit? 2) How many times do they need to be seen? Our model reveals an exponential growth in estimated costs as the numbers of patients and clinic visits increase. Furthermore, both the number of patients enrolled, and the number of clinic visits varied widely even among new molecular entities receiving their initial approval. From the perspective of total pivotal trial costs for new drug approval, estimated costs also increased with the number of trials required.

Overall, the estimated costs are modest for establishing the benefits that will guide the treatment of thousands to millions of future patients. We estimated a median of $48 million per drug and $41 115 per patient enrolled. Note that these costs-per-patient for these trials are sometimes similar to what pharmaceutical companies charge for these same drugs to treat a single patient or a handful of patients after marketing approval.

Our study has limitations. Our pivotal trial costs are credible estimates and not actual trial costs—which could have been lower or higher. For some trial features that were not publicly available we used default values derived from other studies, or a range of assumptions. The study did not include sponsor costs for trial design, contract monitoring, and the medication. While our selection of recent trials was large and varied, it includes only a recent three-year period. These estimates are intended to characterize the costs of obtaining the most important scientific evidence of benefit of a new molecular entity and do not reflect the overall costs of drug development.

Conclusions

At a median cost of $41 115 per patient enrolled, the costs of obtaining this key scientific evidence are modest. Estimated costs were higher for drugs that required a comparison with an already approved and effective drug. They were lowest when the FDA waived the requirements for a control group and replication of the trial evidence.

Contributors Conception and design: TJM, GA, GCA. Data acquisition and analysis: JH, TJM, GCA. Data interpretation: TJM, GCA, GA. Drafting of the manuscript: TJM. Critical revision of the manuscript for important intellectual content: GCA, GA, JH. Final approval of the version to be submitted: TJM, GCA, JH, GA. TJM takes full responsibility for the integrity of the data and analyses.

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Competing Interests Dr. Alexander is past Chair of FDA's Peripheral and Central Nervous System Advisory Committee; serves as a paid advisor to IQVIA; is a paid consultant and holds equity in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.

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IQVIA had no role whatever in the design, analysis, results, and preparation of or review of manuscript content (except for statements about IQVIA). Dr. Alexander's role was negotiating with IQVIA to obtain and pay for a license for Johns Hopkins University to provide access to the data, which had been previously limited to internal use at life science companies.

Data sharing statement

The cost estimates for this study were obtained under license and are not available for sharing.

Patient consent for publication None required

Ethics Approval Declared exempt from review by the Johns Hopkins School of Public Health Institutional Review Board because the source data did not contain identifiable human data.

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Figure 1 Patient enrollment and estimated cost of pivotal trials

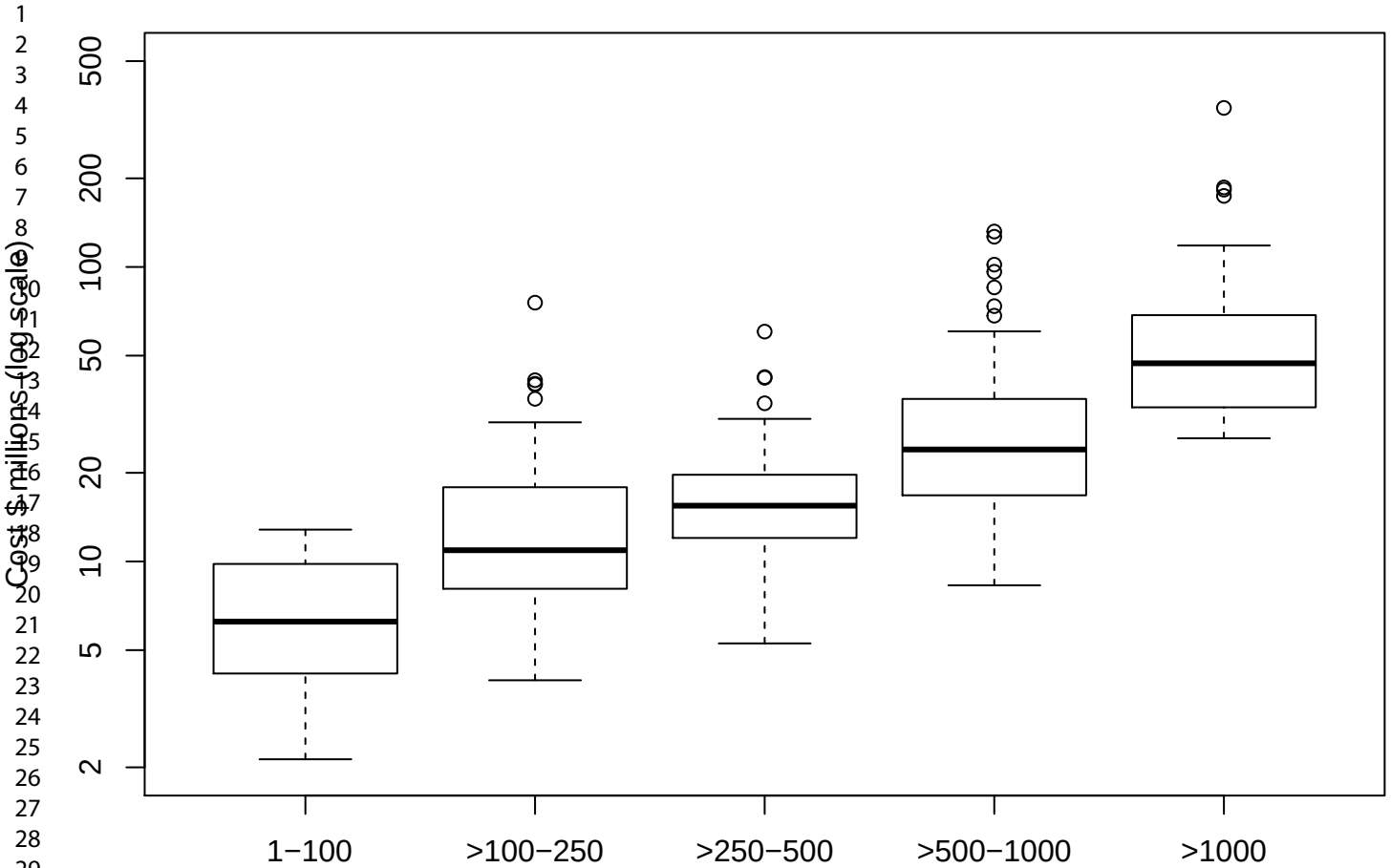
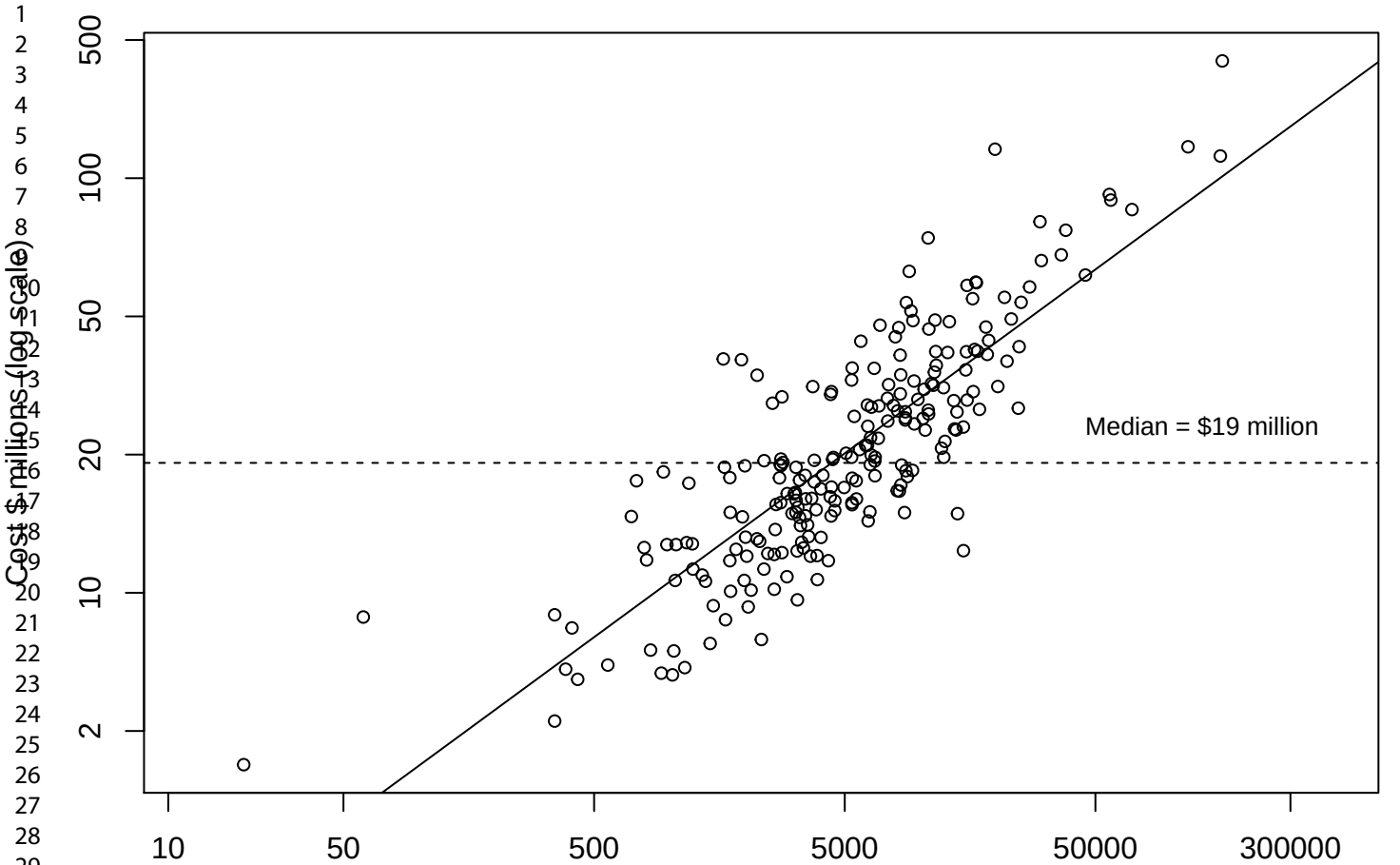


Figure 2. Patient visits vs estimated costs for pivotal trials



Adjusted R−square = 0.696, F = 257.9 on 2 and 222 DF, p < 0.01. Variables log transformed.

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We report the median and interquartile range (IQR) for most variables because they were not normally distributed. For assessing differences between categorical variables, we used a non-parametric test of significance, the Kruskal-Wallace rank sum tests. We used linear regression to model the relationship of trial cost with patients enrolled and patient visits but after log-transforming these variables to achieve a near-normal distribution. The R package for statistical computing, version 3.5.3, was used for all statistical analysis.

Review and Verification

Prior to collecting the data for this study, we conducted sensitivity analysis of the input variables for the CostPro Mid-Level Tool to assess each major variable and whether default values were calculated on the basis of the underlying source data from clinical site contracts. Some variables, such as the countries where trial sites were located and the specific disease condition being treated, proved to have a marked effect on estimated costs. Next, we tested the CostPro tool to compare our estimating methods with some of the available published estimates and determined that they were similar. Finally, we reviewed our preliminary methods and results with experienced clinical trialists with hands-on experience working with trial cost estimates.

Patient and Public Involvement

No patient or public involvement.

Results

Our data include 101 new drugs and 225 pivotal clinical trials that enrolled 156 140 patients who were studied for treatment effects in 2 241 401 clinic visits. Characteristics of the source trials data are shown in table 1.

Table 1 Patients, trials, and drug totals in pivotal trials

Totals by approval year				
	2015	2016	2017	Total
Drugs	40	19	42	101
Trials	86	52	87	225
Patients	69 050	28 111	58 979	156 140

Totals by trials per drug		
Trials per drug	Number of drugs	Total patients
1	45	49 022

2	29	32 157
3-11	27	74 961

Overall, the estimated cost of trials supporting the approval of 101 approved drugs was a median of $48 million (IQR $20 million - $102 million). The estimated costs per drug and by therapeutic area are shown in table 2. Each individual pivotal trial cost a median of $19 million (IQR $12 million - $33 million). The estimated cost per patient was $41 413 (IQR $29 894 - $75 047), and each patient visit to the study clinic cost an estimated median of $3685 (IQR $2640 - $5498).

Table 2 Per drug estimated trials costs by therapeutic area

Therapeutic area	Drugs	Median (IQR), US$ in millions
Blood	2	6 (4 - 8)
Cardiovascular	6	141 (74 - 183)
Central Nervous System	14	42 (16 - 85)
Dermatology	9	50 (31 - 77)
Endocrine/metabolism	12	72 (14 - 144)
Genitourinary	4	23 (12 - 37)
Gastrointestinal	7	31 (15 - 63)
Infectious	9	54 (26 - 102)
Musculoskeletal	2	68 (48 - 87)
Oncology	30	45 (29 - 72)
Ophthalmological	3	36 (34 - 44)
Respiratory	3	91 (73 - 110)
Overall	**101**	**48 (20 - 102)**

Costs per drug varied substantially by the number of pivotal clinical trials conducted to support marketing approval. Costs were generally lowest when the requirement for replication was waived and a single trial accepted. Overall, 45/101 (45%) of drugs were approved with a single trial with a median cost of $28 million (IQR $13 million – $62 million). As might be

expected, the replication requirement for 2 trials nearly doubled the estimated cost per drug of 29 other drugs to a median $45 million (IQR $28 million - $69 million). In addition, 27 drugs were approved with 3-11 clinical trials each at an estimated overall median cost of $91million (IQR $56 million - $128 million) per drug. The reason for three or more trials was because approval was sought for several closely related indications, often combination or adjuvant therapy.

From an individual clinical trial perspective, the largest single influence on estimated cost was the number of patients needed to establish the treatment effects. Although the trials enrolled a median of 495 patients there was wide variation, ranging from 4 patients to 8446 patients.The differences and variability within patient enrollment categories are shown in the boxplots in figure 1. It also shows that there were often outliers to the median estimates even after plotting the data on a log scale.

One factor requiring more patient enrollment was when already approved drugs were known to be effective for the indication sought. One measure of the availability of other effective drugs was the need for an active drug comparison group rather than an inactive placebo. The 62 trials with an active drug control group enrolled a median of 653 patients, compared to 547 patients for placebo control, and 145 patients in uncontrolled trials.

While the number of patients required was the most important cost driver, we also observed variation in the trial cost per patient. Treatments varied in intensity from eye drops and skin creams to infusions of multiple oncology drugs. Table 3 shows how cost per patent varied by therapeutic area.

Table 3. Per patient estimated pivotal trial costs by therapeutic area

Therapeutic area	Trials	Median (IQR), US$		
Blood	2	310 975	(200 213	- 421 738)
Cardiovascular	6	34 857	(22 922	- 50 540)
Central nervous system	33	39 467	(31 825	- 67 988)
Dermatology	21	24 861	(19 523	- 30 573)
Endocrine/metabolism	52	40 612	(34 874	- 63 420)
Genitourinary	7	39 640	(23 179	- 47 100)
Gastrointestinal	12	27 887	(25 633	- 55 687)
Infectious	31	37 175	(31 497	- 49 283)
Musculoskeletal	3	58 212	(34 811	- 63 447)
Oncology	39	100 271	(80 880	- 155 714)
Ophthalmological	9	23 893	(16 990	- 29 894)
Respiratory	10	53 590	(39 062	- 59 814)
Overall	225	41 413	(29 894	- 75 047)

The second-ranked influence on the estimated cost of the pivotal trials was the number of clinic visits required for screening, baseline randomization, treatment, and benefit assessment. The pivotal trials had a median 11 trial visits (IQR 8 - 17) and ranged from 2 to 166 visits. Each additional trial visit added a median of $2 million (IQR $1 million - $3 million) to the overall estimated trial cost. More trials visits could reflect greater intensity of treatment as well as longer duration of treatment or observation.

The results of linear regression predicting estimated trial costs based on the number of enrolled patients and the number of trial visits are shown in figure 2. This combination of just these two variables into individual patient clinic visits explained 69% of the variation (R^2) in estimated costs of pivotal trials. Both dependent and independent variables were log transformed to normalize the distribution. Analysis of variance showed the number of patients explained more than three times as much variation as the number of visits. Additional regression details are shown in figure 2.

Discussion

Our study shows that the cost burden of conducting pivotal trials is driven by two central questions: 1) How many patients are needed to show a drug benefit? 2) How many times do they need to be seen? Our model reveals an exponential growth in estimated costs as the numbers of patients and clinic visits increase. Furthermore, both the number of patients enrolled, and the number of clinic visits varied widely even among new molecular entities receiving their initial approval. From the perspective of total pivotal trial costs for new drug approval, estimated costs also increased with the number of trials required.

Overall, the estimated costs are modest for establishing the benefits that will guide the treatment of thousands to millions of future patients. We estimated a median of $48 million per drug and $41 115 per patient enrolled. Note that these costs-per-patient for these trials are sometimes similar to what pharmaceutical companies charge for these same drugs to treat a single patient or a handful of patients after marketing approval.

Our study has limitations. Our pivotal trial costs are credible estimates and not actual trial costs—which could have been lower or higher. For some trial features that were not publicly available we used default values derived from other studies, or a range of assumptions. The study did not include sponsor costs for trial design, contract monitoring, and the medication. While our selection of recent trials was large and varied, it includes only a recent three-year period. These estimates are intended to characterize the costs of obtaining the most important scientific evidence of benefit of a new molecular entity and do not reflect the overall costs of drug development.

Conclusions

At a median cost of $41 115 per patient enrolled, the costs of obtaining this key scientific evidence are modest. Estimated costs were higher for drugs that required a comparison with an already approved and effective drug. They were lowest when the FDA waived the requirements for a control group and replication of the trial evidence.

Contributors Conception and design: TJM, GA, GCA. Data acquisition and analysis: JH, TJM, GCA. Data interpretation: TJM, GCA, GA. Drafting of the manuscript: TJM. Critical revision of the manuscript for important intellectual content: GCA, GA, JH. Final approval of the version to be submitted: TJM, GCA, JH, GA. TJM takes full responsibility for the integrity of the data and analyses.

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Competing Interests Dr. Alexander is past Chair of FDA's Peripheral and Central Nervous System Advisory Committee; serves as a paid advisor to IQVIA; is a paid consultant and holds equity in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.

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IQVIA had no role whatever in the design, analysis, results, and preparation of or review of manuscript content (except for statements about IQVIA). Dr. Alexander's role was negotiating with IQVIA to obtain and pay for a license for Johns Hopkins University to provide access to the data, which had been previously limited to internal use at life science companies.

Data sharing statement

The cost estimates for this study were obtained under license and are not available for sharing.

Patient consent for publication None required

Ethics Approval Declared exempt from review by the Johns Hopkins School of Public Health Institutional Review Board because the source data did not contain identifiable human data.

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Caption for Figure 1

Kruskal-Wallis chi-square = 110.1, df = 4, p-value < 0.01

Caption for Figure 2

Adjusted R-square = 0.696, F = 257.9 on 2 and 222 DF, P < 0.01. Variables log transformed.

Figure 1 Patient enrollment and estimated cost of pivotal trials

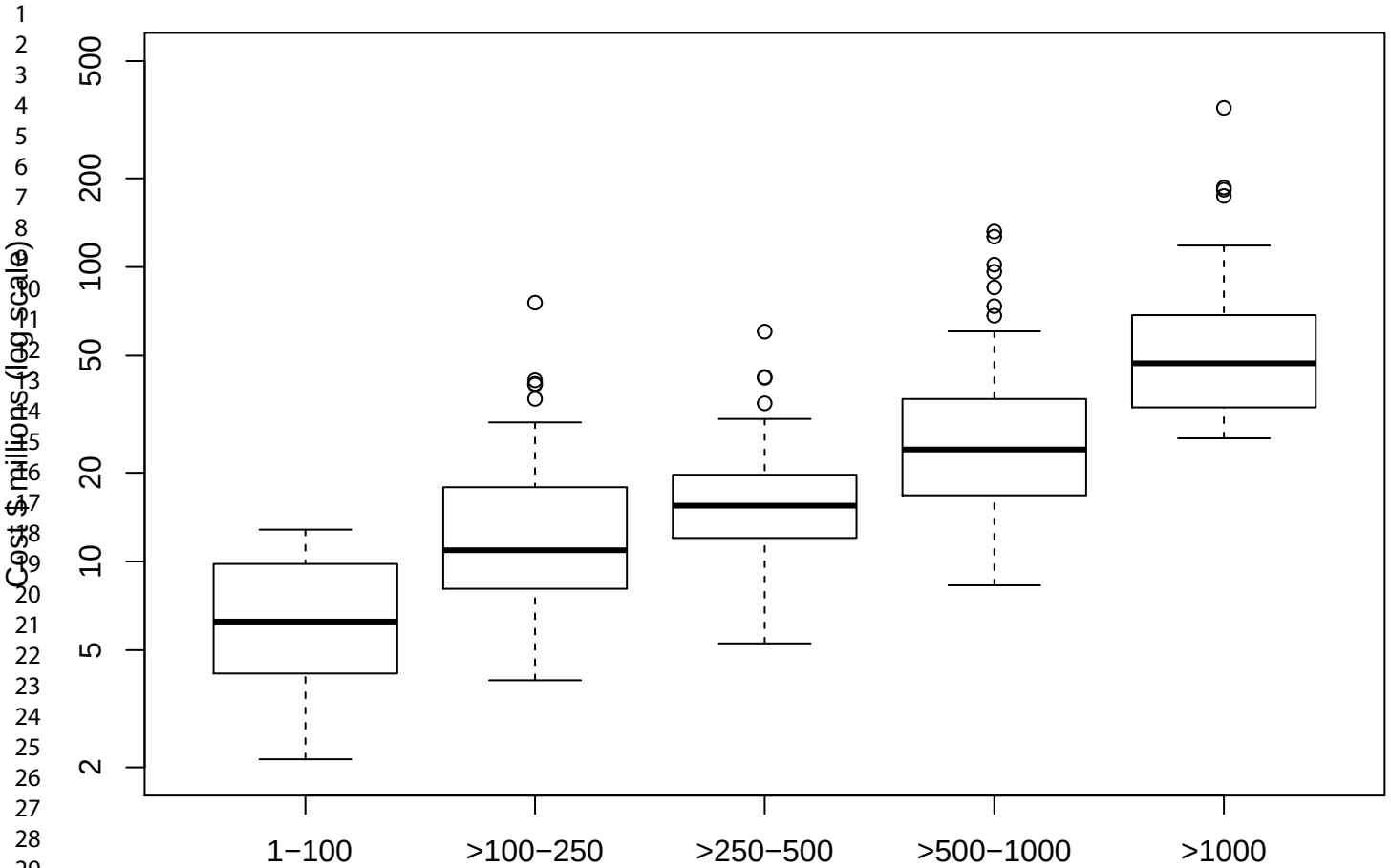
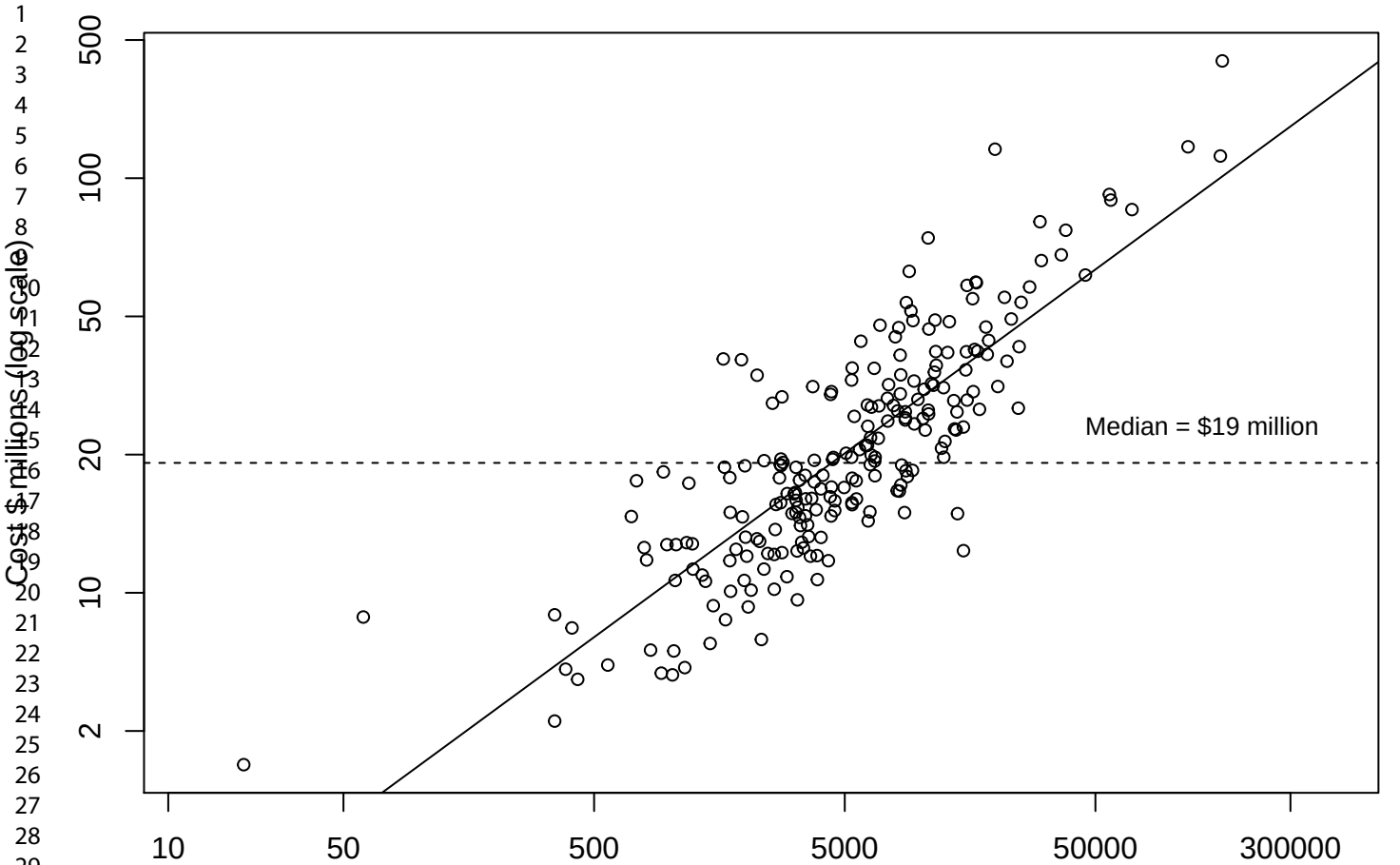


Figure 2. Patient visits vs estimated costs for pivotal trials



Adjusted R−square = 0.696, F = 257.9 on 2 and 222 DF, p < 0.01. Variables log transformed.